

# Pregnancy and Marfan syndrome

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Pregnancy in women with Marfan syndrome (MFS) presents challenges to the clinician and the patient due to the increased incidence of maternal complications and involvement of the fetus, and deserves special consideration. The leading cause of morbidity and mortality in MFS is aortic dissection. This article presents an extensive review of available clinical information and provides recommendations for the management of patients with MFS during pregnancy.

**Keywords:** Marfan; syndrome; pregnancy; aortic dissection



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## Introduction

Marfan syndrome (MFS) is an autosomal dominant hereditary disorder of the connective tissue, in which involvement of the cardiovascular, skeletal, ocular and other systems may be present (1-4). Pregnancy in MFS presents challenges to the clinician and the patient due to the increased incidence of maternal complications and involvement of the fetus, hence deserving special consideration.

## Epidemiology and etiology of MFS

In the United States alone, estimated prevalence of MFS is 1 in 5,000, affecting both genders equally (2,5). Eighty percent of patients have some form of cardiovascular involvement, including aortic dilatation, aortic regurgitation and mitral and tricuspid valve prolapse with or without regurgitation (2,4,6). Although in the past life expectancy was reported to be greatly reduced, significantly better life expectancy due to improved medical and surgical treatment has been recently described (7). The leading cause of morbidity and mortality in MFS is aortic dissection (AoD) (1,4,8-10).

MFS is caused by a mutation in the gene for MFS (FBN1) on chromosome 15q21, encoding the extracellular matrix

protein fibrillin-1 (1,2). Recently, heterozygous mutations have also been identified in the gene encoding tissue growth factor- $\beta$  receptor 2 (*TGFBR2*) on chromosome 3p24.2-25 (11). MFS segregates as a dominant trait in ~70% of families and the remainder of cases is caused by de-novo mutations. The diagnosis is based on the Ghent criteria, published in 1996, later revised to take into account many individuals with MFS who do not have the FBN1 mutation (*Table 1*) (5,6). Major criteria are found infrequently in the general population and therefore carry limited diagnostic sensitivity, but high specificity. The diagnosis may be challenging and should involve a multidisciplinary approach due to multisystem involvement, as well as clinical genetics. Unfortunately, MFS often remains undiagnosed prior to pregnancy and is recognized only after life-threatening complications occur in pregnancy or after the delivery.

## Cardiovascular risk of pregnancy in Marfan syndrome

### Risk for the mother

The most serious complication in patients with MFS is AoD, and the risk is substantially increased during pregnancy and the post-partum period (PP) (4,8-10,12,13). Increased risk is caused by maternal cardiovascular changes such as

**Table 1** Ghent diagnostic nosology

System	Major criteria	Minor criteria
Skeletal	At least 4 of the following features:  Pectus carinatum Pectus excavatum requiring surgery ULSR <0.86 or span: height >1.05 Wrist and thumb signs Scoliosis >20° or spondylolisthesis Reduced elbow extension (<170°) Pes planus Protrusion acetabulae	Two of the major features, or 1 major feature and 2 of the following:  Pectus excavatum Joint hypermobility High palate with dental crowding Characteristic face
Ocular	Lens dislocation (ectopia lentis)	Flat cornea Increased axial length of globe (causing myopia) Hypoplastic iris or ciliary muscle (causing decreased miosis)
Cardiovascular	Dilatation of aortic root	Mitral valve prolapse Dilatation of the pulmonary artery, below age 40 Calcified mitral annulus, below age 40 Other dilatation or dissection of the aorta
Pulmonary	None	Spontaneous pneumothorax Apical blebs
Skin/integument	None	Striae atrophicae Recurrent or incisional hernia
Dura	Lumbosacral dural ectasia	None
Genetic findings	Parent, child or sibling meets these criteria independently  Fibrillin 1 mutation known to cause Marfan syndrome  Inheritance of DNA marker haplotype linked to Marfan syndrome in the family	None

Having one of the features listed constitutes a major criterion or minor criterion for all systems except the skeletal system, where more than one feature is needed. ULSR, upper to lower ratio.

rise in blood volume, heart rate and stroke volume (14) and by hormonally-mediated histologic changes in the diseased aortic wall. Based on two recent systematic reviews (15,16) MFS is still the most frequent cause of pregnancy-related acute dissections.

Increased risk of complications in pregnant women was initially described by Pyeritz *et al.* more than 20 years ago, who reported AoD in 20 out of 32 pregnant

women with MFS (17). Later, Elkayam *et al.* (12) reported on 15 additional cases, of which 10 had cardiovascular complications mostly AoD, and mainly in the second and third trimesters, but also few days after conception or during labor and after delivery, including two maternal deaths. Immer *et al.* (18) described 16 cases of pregnant women with MFS with type A dissection (mean aortic root diameter of 4.8±0.8 cm) with no maternal death, however,

fetal deaths were reported in three cases. Goland *et al.* (9) in a review of 39 cases of pregnancy related complications described AoD in 29, involving the ascending aorta (19 cases), descending aorta (8 cases) or both (2 cases), 8 of these women were undiagnosed with MFS prior to the occurrence of aortic complications (9,19-22). Five patients developed an AoD before week 20 of gestation (13–20 weeks), 18 patients at 24–40 weeks, and 6 after delivery. One patient developed an extension of distal dissection at 1 week PP, chronic dissection remained unchanged in two patients and intracranial hemorrhage occurred PP in two cases. Nineteen of the patients were diagnosed with dilatation of aorta prior to pregnancy and four had a history of aortic surgery. Maternal and fetal mortality were reported in two patients, and fetal loss in two cases despite of maternal survival. Reviewing the English literature between 1995 and May 2017 (23-35), we found 38 additional MFS cases with pregnancy-related complications (36-52). Sixty-three women developed an acute AoD: 59% of the ascending aorta, 32% of the descending aorta and both in 9%. Vast majority occurred after 24 weeks gestation (61%) or up to 3 months postpartum (23%) and the rest between 7–23 weeks. In addition, 8 patients developed progressive dilatation of the ascending aorta requiring surgery during pregnancy. In two women with chronic distal dissection, it remained stable during pregnancy in one and extended 1 week postpartum in the other. Three patients experienced intracranial hemorrhage postpartum (30 min, 6 weeks and 57 days after delivery). Maternal mortality was reported in 7 out of 73 cases with available outcome information, 3 died from immediate complications of AoD and 4 had delayed death from 2 months to 8 years (1 patient each from intracranial hemorrhage, subarachnoid hemorrhage, recurrent AoD and SBE). Three cases of severe morbidity were reported: one of paraplegia after aortic repair due to type B dissection and two with multi-organ failure, requiring ECMO support in one. Majority of the patients in whom a dissection occurred during pregnancy delivered their babies by C-section. Information regarding the time of surgery was available in 50 patients and was prior to delivery in 8 women, immediately after C-section in 22 and hours to 1 month after delivery in the rest of the patients.

The incidence of pregnancy-related AoD in patients with MFS has varied among available publications and most reports have described severe complications. This information however, is likely to provide an over representation of pregnancy-related complications caused by a bias toward reporting complicated rather

than uncomplicated cases. Such an assumption is supported by several reports of significantly lower rate of complications. Pyeritz *et al.* (17) showed only a low risk for maternal complications and death in a retrospective analysis of 105 pregnancies in 26 patients with MFS and a prospective follow-up of 10 patients who had minimal or no pre-existing cardiovascular disease. Rossiter *et al.* (19) prospectively evaluated 45 pregnancies in 21 women with MFS and reported AoD in only 2 cases (4.4%) while the rest who had aortic diameter <4.0 cm tolerated pregnancy well. More recently, Lipscomb *et al.* (20) reported the outcome of 91 pregnancies in 36 women with MFS and described AoDs in pregnancy in 4 (4.4%) with two others requiring aortic surgery following delivery. Meijboom *et al.* (53), followed prospectively 127 women with MFS and compared aortic root diameter changes during 33 pregnancies with those of 22 matched childless women. During 6.4 years of follow-up, no significant difference in growth of the aortic root was obtained and only one woman with previous type A dissection developed type B dissection during her 2<sup>nd</sup> pregnancy. The authors concluded that pregnancy is relatively safe in women with an aortic root diameter of <4.0 cm. In a retrospective French study Pacini *et al.* (54) reported 7 aortic complications in 85 women (160 pregnancies; 4%) representing a 5 fold increase in risk of pregnancy related aortic complication compared to that of a group of never pregnant women with MFS. Omnes *et al.* (41) from the same group reported good outcome in 17 women followed prospectively and closely during pregnancy, and an additional case of acute AoD who was referred at the late pregnancy (37 weeks) with an increase in the aortic diameter from 47 to 50 mm between weeks 24 and 37 of pregnancy. Donnelly *et al.* (55) reported on a cohort of 69 women with MFS, without pregnancy-related AoD. Kuperstein *et al.* (51) reported on 2 cases of postpartum AoD in a cohort of 19 women with MFS (6.5%), 1 case of type A dissection in a woman with a dilated aortic root who declined  $\beta$ -blockers and 1 case of type B dissection. Hassan *et al.* (56) in a large, population-based US cohort reported on 339 pregnant women with MFS describing 6 pregnancy-related AoDs (1.8%) and 1 related death. The most recent large longitudinal observational study (GenTAC) published by Roman *et al.* (57) reported outcomes of 227 pregnancies in 97 women. Pregnancy-related aortic complications occurred in 10 women (4.4%); AoD in 8, coronary artery dissection in 1 and aortic growth >3 mm in 2. However, information on the aortic size before pregnancy was not available.

Several studies focused on the potential growth of the aorta in pregnant women with MFS and have reported contradictory results (19,22,51,53,55). Rossiter *et al.* (19) prospectively evaluated 45 pregnancies in 21 women with MFS and found AoD in only 2 while the remaining women with an aortic diameter <40 mm tolerated pregnancy well without an increase in aortic diameter. Meijboom *et al.* (53) found no significant difference in the aortic root growth during 33 pregnancies in 23 patients with MFS (aortic diameter  $\leq$ 45 mm), compared to 22 matched childless women in a 6.4-year follow-up. In contrary, Donnelly *et al.* (55) described 199 pregnancies in 98 MFS women, there were no acute AoD, but 2 women, developed symptomatic carotid artery dissections. An average increase of 3 mm (0–7 mm) in aortic diameter was observed during pregnancy, which was decreased postpartum, but without complete recovery at 5 years follow-up. The prevalence of both AoD and elective aortic surgery during long-term follow-up was higher in women with prior pregnancy, larger aortic diameter, greater rate of aortic growth during pregnancy, increased number of pregnancies, and no  $\beta$ -blocker therapy and regular follow-up during pregnancy.

In summary, the rates of aortic complications reported in prospective studies appear to reach on average 4.0% (3,19,41,53) and is 2–6% in large retrospective reports including 1,142 pregnancies (20,22,53–58). The expected rate of AoD is ranging from 1% in women with aortic diameter <40 mm to as much as 10% in high-risk patients (those with aortic root diameter >40 mm, rapid dilatation or previous dissection of the ascending aorta) (3,9,53,59). Despite the rare occurrence of AoD in women with MFS and a normal size aorta (3,9,18,59,60), an event-free pregnancy cannot be guaranteed in these women as well (19,20,61,62). Although AoD occurs in most women during the third trimester and the PP, it may also occur at any time of gestation (8,9,59).

### Long-term outcome after pregnancy

Information regarding expected morbidity and mortality after pregnancy should be provided to a woman with MFS who is considering pregnancy. Groenink *et al.* (60) reported 5- and 10-year survival after diagnosis of 95% and 88% respectively and complication free survival of 78% and 66%. Ten percent of the patients developed dissection and 24% underwent prophylactic repair. In patients without aortic complications, mean aortic root diameter was 33 mm and aortic root growth was 0.5 mm/year. In patients who

underwent prophylactic aortic root surgery, mean aortic root diameter was 49 mm and aortic growth 3.6 mm/year. One patient (3%) died post operatively and 10% developed complications at other levels of the aorta. Of the 13 patients who developed AoD, 9 died either before reaching the hospital or perioperatively. Svensson *et al.* (63) and Gott *et al.* (64) reported on a total of 393 patients who underwent aortic surgery for aortic root replacement. Mortality was higher in patients who had urgent or emergent operation. These data clearly indicate that in spite of effective medical and surgical therapy, MFS is associated with increased likelihood of major morbidity and even premature death that also applies to women after successful delivery. The likelihood of such complications is especially high in patients with a history of acute type A dissection but unexpected fatal complications may also occur following prophylactic aortic root or mitral valve surgery (52,53,63).

### Risk for the fetus and obstetric complications

The risk of transmission of MFS to the offspring appears to be at least 50%. Because of the variability in clinical presentation, severe expression of the syndrome can occur in an offspring of a mother with a relatively mild presentation. It should be noted that development of AoD in the mother carries a substantial risk to the fetus (8,9,12,18). Among 71 cases with available information in our review of literature, fetal loss occurred in 7 pregnancies, and stillbirth and brain atrophy in 1 each. Fetal loss was due to termination of pregnancy prior to aortic repair in 2 cases, intrauterine death in 3 (17–24 weeks) and fetal loss as a result of maternal death in 2.

Pregnancy in women with MFS has been shown to be associated with a high rate (up to 40%) of obstetric complications, such as premature delivery, mainly due to premature rupture of membranes, intrauterine growth restriction, small for gestational age and neonatal mortality (8,9,22,41,51,56,65,66).

### Prenatal diagnosis of Marfan syndrome

Molecular genetic testing can be used for the prenatal diagnosis of MFS (67–69). It can be accomplished by chorionic villus sampling or amniocentesis in affected families. In addition to prenatal diagnosis, preimplantation diagnosis using *in vitro* fertilization is possible when the parent's mutation is known. In addition to the genetic testing, which can be done in early gestation,

echocardiography may be used in the 3<sup>rd</sup> trimester to diagnose cardiac manifestations of MFS in the fetus.

### Preconception counseling

Unfortunately, based on previous published data, preconception counseling in women with known MFS is often not done and in many cases the syndrome is diagnosed for the first time during pregnancy or the PP following the development of complications (22). Pacini *et al.* (54) reported seven aortic complications in 160 pregnancies in women with MFS (4%). Diagnosis of MFS was made during pregnancy in three women, at time of surgery in two other women, and as late as 2 years after surgery in the last two patients. As a result, of late diagnosis none of these women was followed as recommended and/or treated with  $\beta$ -blockers. In line with these studies our review of published literature from 2009 indicated that almost half of the pregnant women were diagnosed with MFS only after occurrence of aortic complications (8).

The management of pregnancy in women with MFS should ideally be started prior to conception. The maternal and fetal risk should be assessed and discussed by a multidisciplinary team including a cardiologist, obstetrician and genetic specialist (59). Women should be counseled about potential pregnancy-related complications and should also be informed about the possibility of prenatal diagnosis using both genetic testing and fetal echocardiography (68-70). Prenatal genetic testing could be used in cases when the result will guide parent's decisions regarding either continuation or termination of pregnancy.

During the preconception consultation, the woman and her family should be informed about possible morbidity during and after pregnancy. The patient should undergo careful evaluation for all cardiovascular abnormalities including valvular pathology, left ventricular function, diameter of the aortic root and the ascending and descending aorta using transthoracic and when needed transesophageal echocardiogram (8,9,59). Evaluation of the distal aorta is especially important in patients with dilated proximal aorta and those with the history of surgical repair of the proximal aorta, who have been shown to be at increased risk of distal AoD (71,72). Either computed tomography (CT) or magnetic resonance imaging (MRI) can be used for a precise assessment of the aortic size and anatomy before pregnancy (59,72,73). Expected risk of aortic complications can be estimated based on the presence of aortic root dilatation (>4.0 cm), rapid increase in aortic

diameter or previous dissection of the ascending aorta (18,19,59,74). Patients should also be informed that dissection in pregnant women with normal sized aortas have been reported (20,61), indicating that event-free pregnancy cannot be guaranteed to any patient with MFS and that AoD can occur in any stage of gestation as well as in the PP period. Most often AoD occurred in MFS women in their 3<sup>rd</sup> decade of life, it is advisable therefore, to plan a pregnancy at a younger age (7,18). Patients should be told of the need for a close follow up and treatment with a high dose beta-blockers during pregnancy and the PP period (8,10,59) and be educated of symptoms related to AoD and the need for an immediate care. In addition, women should be informed that previous aortic surgery cannot guarantee uneventful pregnancy and cannot eliminate the risk of recurrent dissection in other parts of the aorta. Elective aortic root replacement can be performed with low morbidity and mortality (64,75,76). For this reason, women with MFS with indications for elective surgery should undergo aortic root replacement prior to pregnancy (10,74).

### Surgical treatment and pregnancy

#### Preventive aortic surgery before pregnancy

The 2011 European Society of Cardiology (ESC) guidelines on management of cardiovascular disease during pregnancy call for prophylactic elective surgery to prevent AoD in women with MFS contemplating pregnancy with aortic root dilatation >45 mm, with the proviso that there is still a risk of dissection even after surgery (59). In patients with aortic diameter of 40–45 mm, considerations for surgical intervention were recommended in cases with rapid growth and a family history of premature AoD. The 2010 American guidelines recommend avoiding pregnancy or attempting aortic root replacement before pregnancy if the aortic root is >40 mm (73), and the recent [2014] Canadian Cardiovascular Society guidelines recommend prophylactic aortic replacement at an aorta diameter >40 mm with or without additional risk factors (77). Although previous studies reported favorable maternal and fetal outcomes during pregnancy with aortic enlargement <45 mm, stricter recommendations by American and Canadian guidelines are probably based on the fact that there is no completely safe aortic root diameter in pregnancy (8,18-20) and the suggestion of some investigators of reducing the threshold for elective aortic root replacement in non-pregnant women compared to men (53) and by others of using an indexed



adjusted aortic diameter for BSA of 2.75 cm/m<sup>2</sup> in small women as a threshold for surgery (72,78).

A valve-sparing aortic root replacement (the David's and Yacoub's procedures) in patients with anatomically normal valves has been advocated in patients with MFS (73,79,80). Although long-term survival has been favorable and the rate of complications low, the durability of this procedure may be somewhat limited, with 17–20% of patients requiring re-operation by 10 years (81). Thus, this technique can be a reasonable alternative for pregnant women and women in the child bearing age who are planning pregnancies and are willing to accept the risk of possible re-operation in the future.

### Surgery for aortic complication during pregnancy

Cardiac surgery during pregnancy is associated with high risk to the fetus and could also increase the risk to the mother. Recent publication describing urgent open heart surgery for severe valvular disease in 12 pregnant women with MFS reported maternal mortality of 8.7% and extremely high intrauterine death (10 out of 12) (82). Yates *et al.* (48) reported in 2015 on a series of 11 women who had aortic surgery including aortic root and/or valve replacement during pregnancy (median gestational age 19 weeks) without maternal death, but high fetal mortality of 27%. Another recent data suggests low maternal mortality (1.47%) similar to that associated with non-emergent cardiac surgery in non-pregnant women (83).

Since the risk associated with emergency operations for AoD or rupture is high, a progressive >5 mm dilation of the aorta during pregnancy has also been proposed to mandate an elective surgery either after a therapeutic abortion (up to 20 weeks) or during pregnancy (8,59,62,83). Successful surgery during gestation or shortly after delivery has been described in a number of women for a marked dilatation of the aorta and for AoD (14,18,21,48,61,83). Because of the increased fetal loss associated with cardiac surgery during pregnancy (9,18,48,61,83–85), a C-section should be done before or concomitantly with thoracic surgery in cases where fetal maturity can be confirmed (17,18,59). Termination of pregnancy should be considered when AoD occurs early taking in account a significant risk of fetal complication and loss (48). In our review of literature out of seven cases of fetal mortality it was reported early (before 20 weeks of gestation) in 4: due to termination of pregnancy in 2 (1 hysterectomy, 1 elective abortion) and due to intrauterine fetal death in 2 women.

Optimal perioperative management including full maternal and fetal monitoring, attention to cardiopulmonary bypass, pulsatile perfusion, near-normothermia, maintenance of high flow rate (>2.5 L/min/m<sup>2</sup>) and mean blood pressure >70 mmHg, hematocrit >28%, avoidance of maternal hypoglycemia and hypoxia, placing the patient in the lateral position during CPB to avoid inferior vena cava compression and avoidance of vasoconstrictors, all have been reported to decrease risks for both the mother and the baby (48,82–84).

Recently the thoracic endovascular aortic repair has been introduced for the management of patients with type B AoD. Data from the International Registry of Acute AoD have suggested a lower mortality over a 5-year period associated with this technique compared with medical therapy (86). Only limited information from isolated case reports is however, available on the use of this technique as a bridge to open surgery in pregnant women with MFS.

### Medical therapy

A number of studies have demonstrated that  $\beta$ -blockers slow the growth of the aortic root and significantly reduce rates of aortic dissection and death (55,87). However, a recent meta-analysis of all prospective trials demonstrated that although  $\beta$ -blockers were effective in aortic root growth rate reduction in patients with MFS, they had no influence on rate of dissection and final aortic size (88). The applicability of these findings to pregnancy, which is associated with changes in the aortic wall and enhanced risk of dissection, needs to be studied in more detail, but on the basis of available information, the prophylactic use of  $\beta$ -blockers during pregnancy seems to make a good clinical sense. The use of selective  $\beta$  receptor blockers is recommended during pregnancy at a dose titrated to reduce heart rate by at least 20 bpm with a close follow-up to detect intra-uterine growth restriction (8,10,13,59). A favorable effect of angiotensin receptor blockers (ARB) leading to a reduction in rate of progressive aortic root dilation in patients with MFS has been reported. The use of ARBs in pregnancy, however, is contraindicated because of potential toxicity to the fetus (89), therefore, ARB's should be switched to  $\beta$ -blockers as soon as contraceptives are stopped and pregnancy is planned. As high blood pressure may increase the risk of aortic complications, strict blood pressure control is recommended for all pregnant women with MFS. The use of nitroprusside for acute AoD during pregnancy may lead to thiocyanate toxicity to the fetus, thus, the gestational use of nitroglycerine or

hydralazine plus  $\beta$ -blockers to control blood pressure is preferred. The use of  $\beta$ -blockers in patients with chronic type B dissection has been shown to reduce the progression of aortic dilatation, hospitalizations and additional aortic procedures (90).

### Follow-up during pregnancy and postpartum

Patients with MFS should be followed during pregnancy by their obstetrician and cardiologist in collaboration. Transthoracic echocardiography (TTE) examination should be performed every 4–6 weeks in patients with aortic diameter of  $\geq 40$  mm, progressive dilation and each trimester in those with normal-sized aorta (59). The American guidelines (ACCF/AHA) recommend monthly or bimonthly echocardiographic measurements of the ascending aortic dimensions in women with aortic dilatation during pregnancy and the first weeks after delivery (73). Postpartum AoD has been described in 16 out of 62 cases reviewed by us (26%) with the latest occurring 4 months after the delivery. Similar findings were reported by Yuan *et al.* (16) who published a literature review of 27 cases of postpartum dissection which occurred from day 1 to day 42 and 41% of them accounted for MFS. Based on this information it seems advisable to extend the follow up of women with MFS for 3–6 months post-partum.

Careful examination, with special attention in order to obtain reproducible serial measurements of all visible parts of the aorta, is critically important for accurate assessment and early detection of important changes in aortic dimensions and at the same time the prevention of false diagnosis of enlargement of aortic diameter (91) which can lead to unnecessary premature delivery and/or surgery. In those with suboptimal TTE visualization, TEE or MRI can be used for assessment (59). Magnetic resonance imaging without gadolinium is considered safe during pregnancy (92).

### Labor and delivery

Vaginal delivery is considered safe in patients with MFS

who have an aortic diameter of  $< 40$  mm (20,59,62). In these patients, C-section should be reserved for obstetrical indications (12,20,62). At the same time, however, to reduce the stress of labor, epidural anesthesia and  $\beta$ -blockers or vasodilators should be used to minimize pain and hemodynamic fluctuation during labor and delivery (14) and forceps or vacuum to shorten the second stage of labor are recommended. It should be noted that lumbosacral dural ectasia is present in about 70% of patients with MFS, anesthesia consultation is therefore advisable planning of the appropriate anesthesia prior to delivery (1).

Patients with aortic dilatation  $\geq 40$  mm or with progressive dilatation of aorta during pregnancy are at high risk for AoD and elective C-section, with epidural anesthesia is preferred to minimize the hemodynamic changes, especially blood pressure peaks associated with vaginal delivery that can induce dissection. When progressive dilatation of aorta occurs early in pregnancy before the fetus is viable, aortic repair with fetus in-utero or termination of pregnancy prior to surgery should be considered. In the case of an urgent need for surgery (type A AoD, progressive dilatation) later in pregnancy to prevent an unfavorable fetal outcome, emergency delivery of the fetus by a C-section should be considered, followed directly by cardiac surgery (8,12,59,61). If all possible cardiac surgery should be performed in a hospital with a neonatal intensive care facility. If elective aortic repair is indicated in the later stage of pregnancy, surgery should be performed, if possible, a few days after delivery (18). Postpartum hemorrhage of the uterine vasculature has been reported in women with MFS and should be anticipated (65,66). Due to increased risk of dissection postpartum, weekly clinical follow-up for high risk patients and monthly for low risk should be considered during at least 4–6 months after delivery (59,62,73). Losartan is not recommended for use during pregnancy. Because of its low molecular weight, excretion into breast milk is to be expected. There are no available reports on the use of the drug during human lactation and the effect on the nursing infant is unknown (93). Because of this beta blocker therapy should be continued for the lactating period.

The key recommendations for the management of pregnancy in women with MFS are presented in *Tables 2,3*.

**Table 2** Pregnancy management in women with Marfan syndrome

Time	Recommendations	Special consideration
Preconception	<p>To assess maternal and fetal risks:</p> <ul style="list-style-type: none"> <li>Past medical and family history</li> <li>Information on the aortic size before conception</li> </ul> <p>To provide proper information on possible prenatal diagnosis</p> <p>Evaluation of the entire aorta: TTE, CT/MRI</p> <p>Initiation of <math>\beta</math>-blockers</p> <p>Consider elective surgery when ascending aorta <math>\geq 45</math> mm</p>	<p>Multidisciplinary care involving cardiologists, obstetricians, genetic specialists</p> <p>TEE when needed, to assess valvular pathology</p> <p>Stop ARB when contraception is stopped</p> <p>Significant AR or MR with LV depression, according to the guidelines for valvular disease</p>
During pregnancy	<p>Serial TTE 4–12 weeks depends on the size of ascending aorta (timing see <i>Table 3</i>)</p> <p>Continue <math>\beta</math>-blockers</p> <p>Type A aortic dissection:</p> <ul style="list-style-type: none"> <li>Unurgent surgery is required</li> <li>Viable fetus: c/s followed by aortic surgery</li> <li>Non-viable fetus: aortic surgery with fetus-in-uterus</li> </ul> <p>Type B dissection:</p> <ul style="list-style-type: none"> <li>Conservative treatment with attention to fetal monitoring</li> </ul>	<p>Use TEE and MRI without gadolinium when needed for optimal visualization</p> <p>Preferable Metoprolol with target HR—reduction of 20% of rest HR</p> <p>Fetal monitoring with attention for fetal growth</p> <p>Strict control of BP</p> <p>Multidisciplinary care management including obstetricians, fetal care, cardiothoracic/vascular surgeon and anesthetists. Optimal perioperative management including full maternal and fetal monitoring, attention to cardiopulmonary bypass, pulsatile perfusion, etc. Serial assessment of the aorta with MRI without gadolinium, thoracic endovascular aortic repair can be considered in selected cases by an experienced team</p>
Delivery	<p>C-section with the ascending aorta 40–45 and <math>&gt;45</math> mm, vaginal delivery in women with diameter <math>&lt;40</math> mm</p>	<p>Pain management</p> <p>Low threshold for assisted vaginal delivery (forceps, vacuum etc.)</p> <p>Attention to symptoms of possible dissection</p> <p>Caution with epidural anesthesia due to high prevalence of dural ectasia</p> <p>Timely diagnosis and management of PPH</p>
Postpartum	<p>Continue <math>\beta</math>-blockers</p> <p>Clinical aortic follow-up during at least 2 months (up to 6 moths)</p> <ul style="list-style-type: none"> <li>High risk—weekly</li> <li>Low risk—monthly</li> </ul>	<p>Women's education is essential: to seek immediate medical attention when symptoms of aortic dissection occur</p>

ARB, angiotensin receptor blockers; TTE, transthoracic echocardiography; AR, aortic regurgitation; MR, mitral regurgitation; LV, left ventricle; HR, heart rate; BP, blood pressure; PPH, post-partum hemorrhage.



**Table 3** Management strategies in pregnant women with Marfan syndrome based on the size of the aorta

Aortic size (mm)	Follow-up	Delivery
<40	Follow-up monthly	Vaginal
40–45	Follow-up monthly	Cesarean section
≥45	Prophylactic surgery pre-pregnancy/or during pregnancy in women with rapid growth of the aorta	Cesarean section

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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